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UNDUE ABSORPTION OF LEAD AMONG CHILDREN

a new look at an old problem

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UNDUE ABSORPTION OF LEAD AMONG CHILDREN – A NEW LOOK AT AN OLD PROBLEM

JANE S. LIN-FU, M.D.

THE Surgeon General's Policy Statement on Medical Aspects of Childhood Lead Poisoning released in November, 1970,[1] called attention to an important but neglected subject – the phase of undue absorption of lead (i.e. absorption beyond that which normally occurs from intake of uncontaminated food, water and air) that generally precedes lead-paint poisoning in children. According to the Statement, all children with excessive absorption of lead, as indicated by a blood lead concentration of 40 or more μg per 100 ml of whole blood, confirmed on two separate occasions, should be investigated. Children found to be currently exposed, whether or not diagnosed as having lead poisoning, should be followed, and hazardous sources of lead removed from their environment. By shifting focus from treatment to prevention through early detection and termination of undue exposure, the Statement puts the disease in its proper perspective.

The hazard of lead-paint ingestion among children living in poorly maintained old houses was recognized by the Baltimore Health Department in the early 1930's.[2] In the ensuing years, many reports appeared clearly defining the etiology, pathogenesis, epidemiology, symptomatology, sequelae, methods of screening, diagnosis and treatment.[3-18] Yet until recently symptomatic lead poisoning was recognized only with difficulty even by physicians caring for children in high-risk areas. Many seldom entertained the diagnosis. Others who recognized it considered it a disease inevitable to slum children about which little could be done. Some regarded it as an all-or-none phenomenon: children found to have elevated blood lead levels were either treated for lead poisoning or diagnosed as not having the illness and discharged with no follow-up observation. Among the latter group, many could have been prevented from becoming poisoned if exposure was terminated at this stage. But this logical step of preventive medicine was seldom practiced, despite knowledge that at least three months of fairly steady lead ingestion usually precedes clinical evidence of toxicity in children[5,19] and that the salvage rate is high if action is taken during this period. Thus, for decades this man-made disease was permitted to exist in epidemic proportions in many old cities.

Only a few cities made limited attempts to attack the problem. Interestingly enough, every city that made such an effort demonstrated that increased awareness of lead poisoning among health workers was invariably associated with a rise in the number of cases reported and a decrease in severe cases and fatalities.[9,15,20,21] In spite of these findings, systematic efforts to eradicate childhood lead poisoning were not made until recent years.

Although symptomatic lead poisoning is a common problem among children one to six years old living in old dilapidated houses, undue absorption of lead unassociated with overt evidence of toxicity

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is far more frequent among these children.[22] The problem of childhood lead poisoning has often been reviewed.[8,9,14,23-26] The purpose of this paper is to review briefly lead intake in children, studies of "normal" blood lead levels, the prevalence of undue lead absorption among children living in old urban neighborhoods, and the importance of detecting children in the early stage of undue absorption.

Lead Intake among Children

Lead is a trace element that has no known essential role in the human body.[27] It occurs widely in man's environment, so that exposure to it is almost inevitable, even for fetuses, infants and children.[28,29] Kehoe's classic studies in adults provide the basic information on the normal metabolism of lead in man.[30-32] Studies in children comparable to those of Kehoe are not available. Chisolm has reported a mean fecal lead excretion of 0.132 mg per day in children 12 to 35 months old with no known undue exposure.[5] Barltrop's studies of children 24 to 35 months of age similarly yielded a mean fecal lead excretion of 0.13 mg and an upper limit of normal of 0.18 mg.[33] On the basis of these data, the average daily intake of lead of children one to three years old may be roughly estimated to be 130 to 170 μg.

According to Kehoe, without undue intake, an equilibrium is established between the amount of lead absorbed and excreted, and no net retention results. In adults, as the mean daily intake exceeds 0.5 to 0.6 mg, accumulation of an excessive body burden begins, increasing progressively as long as abnormal intake continues.[30-32] In children one to three years old, 0.3 mg (300 μg) is considered to be the maximum daily permissible lead intake from all sources.[34] Barltrop's studies indicate that a daily intake of 1 to 2 mg for five to six months is sufficient to cause symptomatic poisoning in two-year-old children.[33]

Indexes of Lead Absorption and Toxicity

Many biologic indexes have been used to measure lead absorption and toxicity. These include measurement of lead concentration in blood, urine, feces and hair, and determination of urinary coproporphyrin and delta aminolevulinic acid (ALA), erythrocyte protoporphyrin, hemoglobin, hematocrit and basophilic stippling of red blood cells. In general, blood lead determination, even with its limitations, is accepted as the most valid and reliable indicator of recent excessive lead absorption. Although indexes such as urinary ALA and coproporphyrin are nonspecific, they reflect the response of the organism and are in fact signs of lead toxicity.[35-37] Urinary lead determination requires a 24-hour specimen, and excretion is influenced by renal function, fluid intake, administration of chelates and other factors. Only blood lead will therefore be discussed here as an index of undue lead absorption.

Blood Lead Values

Problems in Interpretation

Blood lead concentration is the result of several equilibria and should thus be interpreted with caution. A single measurement of elevated blood lead value may not indicate current excessive absorption, and a low value does not necessarily exclude a high bone burden of lead. Serial determinations are needed to determine trends. To assess a given blood lead value, the following factors should be considered: hematocrit; intercurrent infection; coincidental bone disease; current or recent excessive absorption of lead; the interval since excessive absorption ceased; and current or recent administration of chelating agents.[14,38] There is also evidence that blood lead values may fluctuate with the season.[22] Finally, different laboratories may use different methods of blood lead determination, and some vary considerably in accuracy.[39]

In the review that follows, blood lead values are given as reported by the investigators, so that some appear in micrograms per 100 ml and others in micrograms per 100 g or micrograms per cent. Values reported in milligrams are converted to micrograms. Blood lead values expressed as micrograms per 100 g will be numerically somewhat smaller than those expressed as micrograms per 100 ml. However, the difference is so small as to have little consequence in relation to natural and analytical variations.

An Erroneous Concept regarding "Normal" Levels

The upper limit of "normal" blood lead has been variously set at 80, 60, 40, 36 and 20 μg per 100 ml of whole blood.[19,22,40-42] Many papers that attempt to define a normal level seem to imply that values not diagnostic of lead poisoning are normal. In fact, most papers equate the lowest blood lead level diagnostic of lead poisoning with the upper limit of normal. A level not associated with overt clinical evidence of toxicity is not necessarily normal; however, most children with increased and therefore "abnormal" blood lead levels are reported as "asymptomatic."[23,41,43] But symptoms from low-level lead intake may have been overlooked because no one knows what to look for, and children are considered asymptomatic when classic symptoms and signs of lead poisoning are absent.

In industrial medicine, it has been widely accepted that the blood lead level below which lead poisoning does not occur is 80 μg per 100 g of blood.[30,44] In 1968, however, an international conference in Amsterdam did conclude that a blood lead level of 70 μg per 100 ml is the upper limit for acceptable lead absorption.[45] Among children, the blood lead level below which overt symptoms of poisoning are seldom encountered is 60 μg per 100 g.[14,24] In the pediatric literature, this level was therefore arbitrarily equated with the upper limit of normal for many years.

Studies in Children

In the past 15 years a number of reports have indicated that 60 μg as the upper limit of normal is too high, although this level is still used by some screening programs as the cut-off point.[15,43]

In 1956 Bradley et al. reported the blood lead levels of 333 children seven to 60 months old living in a congested low-income area in Baltimore.[46] Forty-four per cent of the children had values in excess of 50 μg per cent, a level at which a definite increase in other findings compatible with lead poisoning was observed. Bradley thus suggested that 50 μg per cent be considered the upper limit of normal. He also pointed out that although a number of children with values greater than 50 μg per cent were asymptomatic, while the study was in progress, eight children previously asymptomatic, with blood lead levels of 50 to 80 μg per cent, were admitted to the hospital with lead encephalopathy.

Two years later, Robinson et al. presented a study of blood lead levels of infants and children from the Jefferson Medical College Hospital in Philadelphia.[47] The median blood lead values of infants five hours to six months of age was 15 μg per 100 ml (range of 5 to 31 μg per 100 ml), and that of children six months to 13 years was 27 μg per 100 ml (range of 3 to 54 μg per 100 ml). Since the Jefferson Hospital serves a high-risk neighborhood, it is possible that the higher values were from children who had excessive lead intake even though they gave a negative history.

Despite these two reports, the Statement on Diagnosis and Treatment of Lead Poisoning in Childhood of the American Academy of Pediatrics, issued in 1961, recommended that "two successive determinations of 0.06 mg. per 100 ml. (60 μg.) of whole blood or higher should be obtained for definitely positive findings" in the laboratory diagnosis of lead poisoning.[19]

In 1964 Moncrieff et al. reported that among 80 children who were not mentally retarded and gave no history of pica, all except two had blood lead levels of 36 μg per 100 ml or less. Among 122 children who either were mentally retarded or had severe behavior disorders, 45 per cent had blood lead values greater than 36 μg. Of 40 children with a presumptive but unconfirmed diagnosis of "encephalitis," 30 per cent had values greater than 36 μg. Moncrieff suggested that 36 μg per 100 ml be considered the upper limit of normal. He also discussed the possibility that undue absorption of lead is responsible for mental retardation of "unknown" etiology in some children.[40]

Moncrieff's study prompted Woods et al. to investigate the blood lead level of 30 children who either were said to "put everything in their mouths" or had a history of early normal development followed by mental deterioration. Twelve of these children had blood lead levels of over 40 μg per 100 ml. Five children with cerebral palsy who were never able to put anything in their mouths and had been hospitalized for some years had an average blood lead level of 13 μg per 100 ml, with a range of 5 to 21 μg per 100 ml.[48]

In 1965 Chisolm reviewed the literature and suggested that the limit of "normal" blood lead concentration that had been widely accepted until then should be revised downward to 40 μg per 100 g.[14]

But new standards are seldom readily accepted, and in 1966, Jacobziner stated that 60 μg was used as the upper limit of normal in New York City but admitted that there were "a number of patients with lower concentrations, 0.05 mg. per 100 ml. (50 μg.) or lower, who have severe clinical plumbism."[15]

Further data on lead levels were supplied in 1967 by Gibson et al., who reported their study of 20 mentally retarded children with organic brain damage from known causes. Some were severely immobilized and under close supervision. The mean blood lead concentration of these children was 16.4 μg per 100 g; none had values greater than 40 μg per 100 g, in contrast to a mean blood lead value of 29.6 μg per 100 g among 20 children of normal intelligence, three of whom had values greater than 40 μg and a history of pica. Among 20 children who had mental retardation of unknown causes, the mean blood lead concentration was 32.4 μg per 100 g. Six had values greater than 40 μg and were found to have pica. The authors noted that eight of the nine children with pica and blood lead values higher than 40 μg per 100 g lived in old houses.[49]

In 1969 Blanksma et al. reported the mean blood lead level of 746 Chicago children 10 to 14 years of age—children theoretically past the age at risk for childhood lead poisoning — to be 23.5 μg per 100 ml.[22] Recently, Millar and his co-workers reported that the mean blood lead concentration of 30 children with IQ's of over 70 was 12.3 μg per 100 ml and that of 27 children with IQ's of less than 70 was 14.6 μg per 100 ml.[50]

The studies cited above are largely based on investigation of urban children. An unpublished report by Blodgett et al. entitled "An Inquiry into Certain Aspects of Lead Absorption in Children as a Community Problem," indicates that urban children have higher blood lead levels than rural children. In this study, the mean blood lead values of 19 rural children was 12.5 μg per cent (range of 6 to 24 μg per cent) whereas that of 30 urban children was 25.1 μg per cent (range of 6 to 52 μg per cent). Only two of the rural children but 19 of the urban children had values over 20 μg per cent. This difference in the blood lead levels of urban and rural children is in agreement with findings in adults.[51,52] Scanlon recently reported the lead concentration in the cord blood of urban infants to be 22.1 and that of surburban infants to be 18.3 μg per 100 ml, a difference considered not statistically significant.[53]

Since studies of "normal" blood lead values in children generally use urban children from low-income areas among whom the possibility of undue lead absorption cannot be excluded with certainty, it may be pertinent to review briefly some studies in adults of different occupations and from different geographic areas.

Studies in Adults

In 1947, Kehoe reported that the mean blood lead level was 23 μg per 100 g in a group of Mexican Indians and 27 μg per 100 g in a group of American students.[31]

Blood lead values of adults with and without undue occupational exposure reported by the United States Public Health Service are shown in Table 1.[52]

Table 1. Blood Lead Levels of Selected Populations.*

Type of Population	Mean Blood Lead (μg/100 G) Males	Females
Population without known occupational exposures:		
Remote California mountain residents	12	9
Composite rural U.S.	16	10
Suburban Philadelphia	13	13
Composite urban U.S.	21	16
Los Angeles aircraft workers	19	17
Pasadena city employees	19	12
Downtown Philadelphia	24	18
Population with known occupational exposures:		
Cincinnati policemen (all)	25	
Cincinnati traffic policemen	30	
Cincinnati automobile test-lane inspectors	31	
Los Angeles traffic policemen	21	
Cincinnati garage workers	31	
Boston Sumner-Tunnel employees	30	

*U.S. Department of Health, Education, and Welfare, Public Health Service, Survey of Lead in the Atmosphere of Three Urban Communities, Publication No. 999-AP-12, Jan, 1965.

Kubota et al. recently reported that the mean blood lead concentration of 243 persons from 19 locations in 16 states in the United States was 13.17 μg per 100 ml. The mean values ranged from 7.25 μg to 20.34 μg per 100 ml.[54]

Goldwater and Hoover analyzed 801 blood specimens from residents of 15 foreign countries, and California, New York and Ohio, and found the mean lead concentration to be 17 μg per 100 ml, with a standard deviation of 11.[51] In the United States the mean blood lead values were 17 μg per 100 ml for residents of California, 21 μg for residents of New York City, and 16 μg for residents of Ohio. Blood lead levels of urban subjects were slightly higher than those of the rural subjects.

Thomas et al. reported that the mean blood lead levels of 15 men and 35 women living near the freeway in Los Angeles County were 22.7 μg and 16.7 μg per 100 ml respectively. That of 20 men and 30 women not living near the freeway were 16 μg and 9.9 μg per 100 ml respectively.[55]

"Normal" Levels

In the review above, blood lead levels reported in children are somewhat higher than those reported in adults, with few exceptions. This apparent difference is not surprising since most studies of children use residents of old urban neighborhoods as subjects. Pica is reported in 30 to 50 per cent of young children.[56,57] Today, lead-based paint is still found in 40 to 80 per cent of old houses in many areas,[58] and a single paint chip the size of a thumbnail could easily contain over 50 mg of lead. Investigation of these children to determine "normal" blood lead levels is therefore likely to yield values higher than those reported in adults. The studies of Woods and Gibson,[48,49] though done on a small scale, suggest that children who are physically restricted have essentially the same blood lead levels as adults.

In general, it may be stated that the mean blood lead level of the urban population without undue intake, expressed in micrograms per 100 ml, is between the teens and lower twenties, the upper limit of normal should be no higher than 40 μg per 100 ml and may actually be lower.[40,42]

Prevalence of Undue Absorption of Lead among High-Risk Children

With the arbitrary use of a single finding of a blood lead level of 40 μg or more per 100 ml as evidence of undue absorption, a brief review of the prevalence of this problem among children in old neighborhoods follows. This review is based on data from screening programs in various cities provided to me.

In Baltimore, blood lead levels of 40 or more μg per 100 g were found in 25.3 per cent of the children tested in 1968, in 27.9 per cent of the children in 1969 and in 31.5 per cent in 1970 (Table 2). Greater selectivity in screening during 1969-1970 largely accounts for the increase in this period.

Table 2. Blood Lead Determinations Performed by the Bureau of Laboratories, Baltimore City Branch, State of Maryland, Department of Health, 1968-1970*

Blood Lead Concentration (μg/100G)	1968 No. of Children	1968 % of Total	1969 No. of Children	1969 % of Total	1970 No. of Children	1970 % of Total
0-39	497	74.7	538	72.1	643	68.5
40-49	131	19.7	154	20.7	159	16.9
50-59					68	7.3
60-79	23	3.5	33	4.4	56	6.0
80 & above	14	2.1	21	2.8	13	1.4
Totals	665	100.0	746	100.0	939	100.0

*Data of Dr. Emanuel Kaplan, Bureau of Laboratories, Baltimore City Branch, Maryland State Department of Health.

In Chicago, of 120,000 children under six years of age who were screened between 1967 and 1970, about 4 per cent had values of 50 μg or more per

100 ml, and 16 per cent had values between 40 and 49 μg per 100 ml.*

In New Haven, Connecticut, among 1897 children screened with blood lead determination in 1969 and 1970, 565, or 29.8 per cent, had values of 40 or more μg per 100 ml. Of these, 180, or 9.5 per cent, had levels of 60 μg per 100 ml.†

In Newark, New Jersey, blood lead determinations were done on 594 children in the summer of 1970 by the Department of Public Health and Preventive Medicine, New Jersey College of Medicine and Dentistry. Blood lead values of 40 to 59 μg per cent were found in 31.5 per cent, and values of 60 or more μg per cent in 7.4 per cent.‡

In New York City, of 2648 children from high-risk areas tested in 1969, 45.5 per cent had blood lead values of 40 μg or more per 100 ml, and 12.5 per cent had values of 60 μg or more. These children constitute about 40 per cent of all children tested in that year and are considered to be a fair representation of the entire population screened. In 1970, of 84,493 blood lead specimens analyzed (which represent 97 per cent of the total number of specimens tested for the year), 28.7 per cent showed values of 40 μg or more per 100 ml, 5.9 per cent 60 μg or more, and 2.7 per cent 70 μg or more. The apparent drop in the percentage of children with elevated blood lead levels is probably a reflection of the change from selective screening in 1969 to mass screening in 1970.§

In Philadelphia, 3496 blood lead determinations in children were done in 1970. Some children had multiple blood lead determinations, and the number of children tested is estimated to have been less than 3000. Blood lead values of 40 to 59 μg per 100 ml were found in 666 children and values of 60 μg or more in 524 children.¶

In Washington, D.C., 808 children were tested in a one-week pilot screening program in June, 1970. Of these, 476 were five years of age or younger. Forty-seven children were found to have blood lead levels of 40 or more μg per 100 ml; 44 of them were in the group from one to five years of age. Between October 5, 1970, and March 26, 1971, 1158 two-year-old children were screened at well-child clinics of the city; 255, or 22.0 per cent, had blood lead values of 40 or more μg per 100 ml, 139, or 12.0 per cent, values of 50 or more μg, and 25, or 2.2 per cent, values of 80 or more μg. Separately, of 193 children one to six years old who were found to have pica on screening in neighborhood health centers, 14.0 per cent had blood lead values of 40 or more μg per 100 ml, 7.3 per cent levels of 50 or more μg, and 1.6 per cent levels of 80 or more μg.‖ The wider age range of the children with pica probably accounts for the lower rate of elevated blood lead values as compared to the two-year-olds, among whom the peak prevalence of lead poisoning occurs.

The above figures clearly indicate that the problem of undue absorption of lead is enormous among young children living in old neighborhoods. It should be noted, however, that these figures are probably not accurate representations of the actual prevalence of this problem in high-risk areas. These data represent findings of the initial screening tests; repeat blood lead levels of these children are not available. A slightly elevated blood lead level in a six-year-old child who no longer lives in a home with lead paint and who is not exposed otherwise may merely indicate that he had undue absorption of lead in the past. A repeat test some time later will probably show a gradual decrease. The meaning of an elevated blood lead level in such a child is therefore quite different from that of a two-year-old with pica who lives in an old house with peeling lead paint. Furthermore, in cities that do not have large-scale screening programs, testing is more likely to be done on a preselected population – i.e., children with a history or clinical evidence of lead poisoning or undue lead absorption. But even in Chicago and New York City, with their mass screening, 20 per cent or more of the children one to six years old had blood lead values of 40 or more μg per 100 ml. Thus, one must still conclude that in magnitude the problem of undue absorption of lead among children living in old neighborhoods is matched by few, if any, other pediatric public health problems.

Importance of Undue Absorption of Lead

Undue absorption of lead unassociated with overt evidence of toxicity should be viewed as an entity that is separate from but closely related to lead poisoning, which it almost invariably precedes by some time in children. An exception is acute intoxication resulting from inhalation of lead fumes produced by burning lead-impregnated materials such as battery casings.[2,9] Lead poisoning resulting from culinary use of lead-glazed earthenware also tends to have a shorter course than that due to lead paint when exposure is heavy and on a regular basis.[59]

The importance of recognizing the early stage of undue lead absorption among children has at least three aspects: it is vital for the prevention of lead poisoning; there is the possibility of deleterious effects even in the absence of overt clinical evidence of toxicity; and young children may be especially vulnerable to the toxic effects of lead.

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§Dr. Michael Specter, New York City Health Department.

¶Mr. Raymond L. Tyler and Mr. John Baskin, Accident Control Section, Department of Public Health, Philadelphia, Pa.

‖Mr. Dudley G. Anderson, Accident Prevention Division, Department of Human Resources, Washington, D.C.

A Crucial Step in Prevention

Three to six months of fairly steady ingestion of lead generally precedes the development of clinical manifestation of lead poisoning in children.[5,26] Detection at this early stage and prompt termination of such ingestion will therefore prevent almost all cases of lead-paint poisoning. The concept that blood lead levels not high enough to be diagnostic of lead poisoning or considered toxic are normal and therefore harmless is grossly erroneous and has been immensely costly, for it has been an important deterrent to the successful prevention of lead poisoning in children. Waiting for children's blood lead levels to reach a toxic level before steps are taken to terminate exposure has unnecessarily perpetuated this disease.

Data collected by Sachs in the Chicago Lead Poisoning Clinic in the past four years indicate that, of children found to have blood lead levels of 40 to 49 μg per 100 ml, approximately 75 per cent were known to be exposed to peeling paint and broken plaster in their homes, and 25 per cent gave a definite history of ingestion of such materials. Among children treated for lead poisoning at the clinic in 1969-1970, approximately one out of six had a screening blood lead level of only 40 to 49 μg per 100 ml, with follow-up values ranging from 50 to over 200 μg.* Over 40 per cent of these treated children showed a rise in blood lead levels from the initial values of 40 to 49 μg per 100 ml to 60 or more μg at the first subsequent evaluation. These data indicate that, if left alone, a substantial number of children with initial screening blood lead levels of 40 to 49 μg per 100 ml will eventually have lead poisoning — some within one to two months.

Metabolic Disturbance at Low Level of Absorption

Heavy absorption of lead is known to be toxic and even lethal. But is absorption at a low level harmless? In a review of toxic effects of lead, Hardy stated, "Because all recognized effects of lead in the body are harmful and the individual responses varied, it is a considerable leap to conclude that there is a threshold below which lead damage does not occur. The threshold may be useful in predicting a point below which certain clinical symptoms do not appear, but there is no guarantee that damage does not occur below this level."[60] Beyond such logical reasoning, there is also in vitro evidence that lead interferes with the enzyme system in man at blood levels generally considered normal and safe.

Lead inhibits enzymes that are dependent on the presence of free sulfhydryl groups for their activity, and is particularly noted for its inhibitory action on enzymes involved in heme synthesis.[61] The delta amino-levulinic acid dehydrase (ALA-D), which is responsible for the formation of porphobilinogen from ALA and is widely distributed in tissues, has been the subject of some recent investigations.

Various authors have reported in the past on the inhibitory effect of lead and other heavy metals on erythrocyte ALA-D.[62-65] More recently, a close negative correlation between blood lead concentration and activity of erythrocyte ALA-D was reported by several investigators.[35,50,66,67] A decrease in erythrocyte ALA-D was demonstrable even at blood lead levels considered to be in the range of "normal" (5 to 40 μg per 100 ml), and there appears to be no threshold for the inhibitory effect of lead on ALA-D. These in vitro findings contrast with reports by others that the first measurable increase in urinary ALA is observed only after blood lead rises above approximately 30 to 40 μg per 100 ml, and that the relation between blood lead and urinary ALA values is best described by a curvilinear regression line.[45,68] This apparent inconsistency between the effect of lead on ALA-D activity demonstrated in vitro and the accumulation of the enzyme substrate in the body might be explained by the presence of an enzyme reserve.[68]

So far, in man, studies of the inhibitory effect of lead on ALA-D have been confined to erythrocytes of peripheral blood. In lead-poisoned laboratory animals, this effect has been demonstrated in the brain, liver, kidneys and bone marrow. A correlation between the reduction of ALA-D activity in the blood and in the brain tissues of lead-poisoned animals was also reported by Millar et al., who suggested that children with slightly elevated blood lead levels may have some decrease in brain enzyme activity.[50] This rekindled an unanswered question previously raised by others: Does slight but sustained elevation of blood lead level cause subtle though appreciable impairment of brain functions such as mild retardation and learning defects in young children?

Whether the metabolic disturbances demonstrated in vitro at a low blood lead level are harmful to man remains uncertain. But preliminary analysis of data collected in a study of trace-element pollution of air in 77 midwestern cities indicated a positive relation between the lead dustfall in residential areas and cardiovascular mortality.[69] In laboratory animals given subclinical doses of lead, increased susceptibility to infection has been reported.[29,70]

Possible Damage without Clinical Manifestations

The diagnostic criteria for lead poisoning differ from institution to institution. Some consider clinical manifestations of toxicity a sine qua non in diagnosis; others regard an elevated blood lead level or other biochemical evidence of toxicity (or both) as sufficient. The Surgeon General's Statement recommends that a blood lead level of 80 μg per 100 ml be considered unequivocal evidence of lead poisoning, regardless of the presence or absence of other laboratory findings or clinical manifestation,

*Henrietta K. Sachs, M.D., personal communication, 1970.

and that levels of 50 to 79 μg per 100 ml be considered suggestive of possible poisoning.[1] A crucial question that cannot be answered with certainty and has been responsible for the confusion in diagnosis of lead poisoning is whether lead causes any permanent damage in man in the absence of clinical evidence of toxicity. A closely related question, also unanswered, is whether lead can damage the central nervous system of young children in the absence of overt signs and symptoms referable to that system.

In considering these problems, one must first realize that clinical manifestations of lead poisoning in children, such as anorexia, irritability, drowsiness, apathy, abdominal pains and developmental regressions or delay, are nonspecific and difficult to interpret. Perceptiveness and sound judgment of the parents and physician therefore have a vital role in determining whether a child is labeled "symptomatic" or "asymptomatic." Another consideration is that damage caused by lead may not be immediately apparent. Reports from Australia of a high incidence of chronic nephritis, gouty arthritis, mental impairment and hypertension among patients who had lead poisoning in childhood 10 to 40 years previously indicate that some insults caused by lead do not become evident until many years later.[71,72] Work done by Tepper in the United States has failed to duplicate the Australian reports, however, and there is evidence that nephropathy may be a sequela limited to very protracted lead poisoning in childhood.[14,73]

Several follow-up studies have indicated that, among children who had had either asymptomatic lead poisoning or mild poisoning without evidence of central-nervous-system involvement, many later showed deficits in visuomotor functions and behavior typical of children with "minimal brain dysfunction." Restlessness, short attention span, easy distractibility, impulsiveness and other behavior problems were common. Thus, despite adequate intelligence, most of these children did not do well in school. In these relatively small series of patients, no relation was found between the presence or absence of central-nervous-system involvement initially and eventual intellectual development or psychologic defects.[4,6,9,74]

In a larger series, Perlstein et al. reported that, among 425 children who had had lead poisoning, 39 per cent gave some evidence of neurologic sequelae at follow-up examination.[16] Among 59 children in this group who had had encephalopathic symptoms, 82 per cent were left with handicaps. Pertinent to the question of the toxic effect of lead in the absence of clinical symptoms is the finding that of 58 children treated for asymptomatic lead poisoning, five, or 9 per cent, were observed at follow-up study to be mentally retarded. Admittedly, this is a retrospective study, and one cannot be certain that mental retardation did not antedate lead poisoning in some of these children. In the same study, among 232 children with lead poisoning who initially had gastrointestinal symptoms and who had no evidence of encephalopathy, 19 per cent were later found to be mentally retarded, and 13 per cent to have convulsive disorders. Again, it should be noted that vomiting, often considered a gastrointestinal symptom, may be a sign of increased intracranial pressure.[16]

The above findings, though far from conclusive, suggest that lead may seriously damage the nervous system in children who are "asymptomatic" or have no apparent symptoms or signs referable to that system.

That slow deterioration may occur in a chronic disease such as lead poisoning is suggested by the recent experience of Sachs et al. with "asymptomatic" patients whose parents reported improvement in their behavior and language ability after chelation therapy.[23] This interesting observation, made in an uncontrolled group of patients, is difficult to interpret, but one wonders how many children labeled as "asymptomatic" today are in fact so.

Many others have reported on the bizarre manifestation of central-nervous-system involvement in lead poisoning among young children. Early signs such as withdrawal, frequent crying for no apparent reason, temper tantrums, fearfulness, loss of affection, listlessness, refusal to play, inattention and developmental regression generally precede the onset of the more classic manifestations of encephalopathy. Unfortunately, these early clues are usually recognized only in retrospect. Many children are considered to have behavior problems before the diagnosis of lead poisoning is entertained.[25,46,75-77] It is altogether possible that many who do not progress to the stage of frank encephalopathy are never diagnosed and never treated, and eventually appear in schools with learning disabilities, hyperkinetic syndrome and other behavior problems.

What can happen when children who have had lead poisoning are re-exposed is indicated by data collected by Chisolm and Harris. They found a highly significant correlation between the occurrence of severe neurologic sequelae and re-exposure to lead after recovery from mild encephalopathy. Among survivors of acute lead encephalopathy who continue to be exposed and ingest lead, severe permanent neurologic damage occurred in virtually 100 per cent.[5]

Vulnerability of Young Children to Lead

There appears to be some variation in individual reactions to the toxic effects of lead.[60] Some children with blood lead levels well beyond 100 μg per 100 ml appear "well" and "asymptomatic," whereas others present evidence of neurologic involvement at a considerably lower blood lead level.[41] Other than the seasonal factor, much remains unknown concerning the circumstances that determine

the onset of lead encephalopathy and the toxicity of lead in general in young children.

There has been considerable speculation that young children may be unusually vulnerable to the toxic effects of lead.[60,78,79] In fetal rats, lead is reported to act as a teratogen leading to developmental anomalies of the tail and sacrum.[80] Speculation and animal experimentation aside, lead poisoning in children is clinically somewhat different from that in adults. Evidence of toxicity becomes clinically apparent at a lower blood lead level. Among adults, lead poisoning is stated to occur only when the blood lead level exceeds 80 μg per 100 ml.[30,44] But in children, poisoning has been reported repeatedly at blood lead levels below 60 and even 50 μg per 100 ml.[15,41] Sudden onset of encephalopathy without previous symptoms is not infrequent in children 15 to 30 months old, less frequent in older children, and unusual in adults. On the other hand, the Burtonian blue line and peripheral nerve palsies that are characteristic of adult plumbism are rarely encountered in children. Severe colic, with board-like rigidity of the abdomen, typical of lead poisoning in adults, is seldom seen in children, who tend to have vague and less acute abdominal pains.[9,38,81] These findings are reminiscent of the statement made by Bell in 1924 that "Lead is not only much more toxic to the young and pre-adolescent than to the adults and old throughout the vertebrate kingdom, but also the effects produced by the metal are general in the young and local in the adult."[82] In the 4½ decades since that statement, little progress has been made in the understanding of the toxic effects of lead in humans, particularly in young children.

Research is urgently needed to clarify the many questions that have been raised. What is a "safe" level of lead exposure and absorption? Does a slight but sustained increased body burden of lead permanently damage human beings even in the absence of overt clinical evidence of toxicity? Are young children more vulnerable than adults to the toxic effects of lead? Do genetic disorders such as sickle-cell anemia and glucose-6-phosphate dehydrogenase deficiency, both of which are common in the population at risk, affect lead metabolism and toxicity? There are many others.

In summary, undue absorption of lead is a health problem of alarming proportions among young children living in old dilapidated neighborhoods. Its magnitude is many times that of lead poisoning, an illness already labeled as "epidemic" in many areas.[83] At present, it remains uncertain whether or not lead causes permanent damage in humans at a low level of absorption and in the absence of clinical symptoms. But there is in vitro evidence of metabolic disturbance at such low levels, and some reports suggest that permanent neurologic damage can occur in the absence of overt clinical symptoms. One certainty is that if exposure is not terminated in children with early evidence of undue absorption of lead, many will become poisoned. Detection and termination of the exposure at this stage is therefore an essential step in the prevention of childhood lead poisoning.

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